REMARKS

Claims 17-29 are pending in the application as shown in the paper filed December 16, 2004. Claim 29 is withdrawn as being drawn to a non-elected invention. Claims 17-28 are under active consideration.

Rejection under 35 U.S.C. § 112, first paragraph

Claim 17 is rejected under 35 U.S.C. § 112, first paragraph on the grounds that the amendment filed December 16, 2004 allegedly introduced new matter into the disclosure of the invention. In particular, the Office Action alleges that "[t]he base claim 17 now includes the generic limitation: 'and an adjuvant'" and "there appears to be no support for a composition comprising any generic 'adjuvant' other than 'MF59' or 'alum'" (Office Action, page 3). Applicants respectfully disagree and traverse the rejection.

The use of aluminum hydroxide or MF59 as adjuvants is merely described as a preferred embodiment (see specification, for example, at page 2, lines 5-9). The specification describes additional adjuvants, for example, at page 3, lines 8-15, which include carriers with immunostimulatory properties such as proteins, polysaccharides, inactive virus particles, etc. Further, the specification explicitly states that these other molecules can be used as adjuvants and indicates that any suitable adjuvant well known in the art can be used in the vaccines (see, e.g., page 3, lines 14-15).

Therefore, no new matter was introduced into the specification as a result of the previous amendment, and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph is respectfully requested.

Rejection under 35 U.S.C. § 103

Claims 17-23 and 25-27 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Costantino et al. (Vaccine 10:691-698, 1992) and van der Voort et al. (Infect. Immun. 64:2745-2751, 1996) in view of Paradiso et al. (Dev. Biol. Stand. 87:269-275, 1996). In particular, the Office Action alleges:

> It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine van der Voort's immunogenic group B meningococcal hexavalent outer membrane vesicle vaccine from the group B meningococcal reference strain H44/76 with Costantino's group C *Neisseria meningitidis* oligosaccharide-CRM197 conjugate vaccine comprising the adjuvant to produce the instant invention, with a reasonable expectation of success, because Paradiso et al. expressly taught that it is desirable to mix a group C meningococcal conjugate with outer membrane vesicles prepared from group B meningococcal strains containing an array of proteins and lipids to create a new set of formulation. Since one of skill in the art would readily understand that Costantino's group C meningococcal oligosaccharide-containing vaccine would not induce immunity against group B meningococci, a major causative agent of meningitis, a skilled artisan would have been motivated to produce the instant invention for the expected benefit of not only eliciting antibodies against serogroup C meningococci, but also for eliciting advantageously bactericidal antibodies to, or for covering more than 80% of the group B meningococcal subtypes isolated in many countries as taught by van der Voort et al. With the Costantino's group A and/or C glycoconjugate comprising an adjuvant and van der Voort's group B meningococcal OMV known and available in the art, and given the express teaching or suggestion by Paradiso et al. that 'in the future it will be desirable to mix such a vaccine', i.e., outer membrane vesicles prepared from cells of virulent group B strains, with the group C and/or group A conjugates, one of skill in the art would have readily understood the desirability for 'mixing' Costantino's group C and/or group A glycoconjugate with van der Voort's group B meningococcal outer membrane vesicles. (Office Action, pages 3-4).

Further, claims 22 and 26, which are product-by-process claims including the process limitation, "vesicles are produced by a deoxycholate extraction process," are rejected on the grounds that "Applicants have not shown that the alleged difference(s) in the process results in a product that is structurally different from the product of the prior art. In the instant case, Applicants have not shown that the underlying structure of the prior art group B meningococcal outer membrane vesicles differs from that of the instantly claimed vesicles" (Office Action, page 6).

In addition, claims 24 and 28 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the references of Costantino et al. (Vaccine 10:691-698, 1992), van der Voort et al. (Infect. Immun. 64:2745-2751, 1996), and Paradiso et al. (Dev. Biol. Stand. 87:269-275, 1996), further in view of Granoff (U.S. Patent No. 6,413,520). In particular, the Office Action alleges that "[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add Granoff's ('520) polylactic or polyglycolic acid to

Costantino's composition as modified by van der Voort et al. and Paradiso et al. to produce the instant invention, with a reasonable expectation of success" (Office Action, page 6).

Applicants respectfully traverse the rejections under 35 U.S.C. § 103 on the following grounds.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on Applicant's disclosure." M.P.E.P. § 706.02.

Costantino et al. fails to teach or suggest the use of immunogenic outer membrane vesicles from any strain of *Neisseria meningitidis*, nor the use of a combined vaccine comprising group C meningococcal oligosaccharides and antigens from group B *Neisseria meningitidis*. Moreover, the reference of Costantino can be described as teaching away from the claimed invention in that Costantino suggests producing a protein-saccharide conjugate vaccine against serogroup B *N. meningitidis* by improving the immunogenicity of meningococcus B polysaccharide by coupling to an immunogenic protein (see page 691, col. 2).

The reference of van der Voort et al. fails to cure the deficiencies of Costantino et al. The reference of van der Voort et al. describes a hexavalent outer membrane vesicle vaccine against serogroup B *N. meningitidis*; however, fails to teach or suggest the use of a combined vaccine with serogroup C meningococcal oligosaccharides, nor provides any motivation for using a saccharide-based vaccine.

The Examiner relies on a third reference, Paradiso et al., to provide the motivation to combine the teachings of Costantino et al. and van der Voort et al. However, the reference of Paradiso et al. does not teach combining meningococcal C oligosaccharide conjugates with meningococcal B proteoliposomic vesicles, as recited in the claims, because Paradiso discusses only vaccines comprising meningococcal C polysaccharide conjugates and never discusses meningococcal C oligosaccharide conjugates. Therefore, when Paradiso refers to mixing with "the group C and/or group A conjugates," it is referring to the polysaccharide conjugates described in the article (see pages 271-272 and Table 4, discussing only polysacchrides and polysaccharide conjugates). Paradiso cannot provide the motivation for combining an element

that it never mentioned or referred to. The showing that two references can be combined must be "clear and particular." See *In re Dembiczak* (CA FC) 50 USPQ2d 1614 (4/28/1999).

The reference of Granoff (U.S. Patent No. 6,413,520) also fails to cure the deficiencies of Costantino et al., van der Voort et al. and Paradiso et al. because Granoff also fails to teach or suggest any combination vaccine containing meningococcal C oligosaccharide conjugates and meningococcal B immunogenic outer membrane vesicles.

The specification clearly shows the distinction between polysaccharide and oligosaccharide conjugates in provoking an immune response against *Neisseria* bacteria when used in combination with MenB outermembrane vesicle antigens. As shown in Table 2 on pages 7-8 of the specification, the use of MenC polysaccharides in combination with MenB outer membrane vesicle antigens produces an insignificant anti-MenC antibody response, whereas the use of MenC oligosaccharide conjugates gives good results, both with alum and MF59 adjuvants. This effect is also seen in Table 3 on page 9, where anti-MenC titers differ more than 100-fold (30 vs. >3375). Table 3 also shows that the anti-MenB titer is improved when the MenC oligosaccharide conjugate is used (1500 vs. 5000).

No prior art has been identified which specifically suggests combining MenB outermembrane vesicle antigens with MenC oligosaccharide conjugates as claimed. Thus, the Examiner has not met the burden of establishing a *prima facie* case of obviousness. In the absence of some teaching or suggestion in the cited references concerning production of the claimed combination vaccine described in the present application, the Examiner has presented no more than an improper hindsight reconstruction of the present invention. As stated by the Court of Appeals for the Federal Circuit *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." For at least the above reasons, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above remarks, Applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited. Applicants invite an interview with the Examiner to further prosecution of the case.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

Please direct all further written communications regarding this application to:

Nicole Fortune
Chiron Corporation
Intellectual Property - R440
P. O. Box 8097
Emeryville, CA 94662-8097
Tel: (510) 923-3004
Fax: (510) 655-3542

Respectfully submitted,

Date: August 18, 2005

By: Jenny Buchbinder

Jenny Buchbinder, Ph.D.
Registration No. 48,588
(650) 354-3383

CHIRON CORPORATION
Intellectual Property - R440
P. O. Box 8097
Emeryville, CA 94662-8097